



FACIAL TRANSPLANTATION

Brave New Face

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In her office at the Cleveland Clinic, plastic surgeon Maria Siemionow has been studying the photographs and perusing the medical records of severely disfigured people, looking for the ideal

candidate to undergo what could be the world's first transplantation of an entire face.

Last October, Siemionow and her team became the first to receive approval from the institutional review board (IRB) of a U.S. hospital to proceed with plans to perform the experimental surgery. In London, plastic surgeon Peter Butler has also obtained permission from the Royal Free Hospital's research ethics committee to begin evaluating patients for the procedure. In France, a 38-year-old woman who had sustained a horrific dog bite is recovering after the world's first partial facial transplantation, performed in November by surgeons from Amiens and

Lyon. Other groups in the United States and elsewhere are also hoping to embark on facial transplantation, including a surgeon in China who is reportedly considering such an operation for an 11-year-old girl who was disfigured by acid burns.

"This is a grand human experiment," said Robert L. Walton, a professor of plastic surgery at the University of Chicago. "You really don't know what is going to happen until you actually engage in the experiment."

Fictional treatment of the topic in books and movies, including the 1997 film *Face/Off*, has fueled the public's fascination with facial transplantation, prompting intense

media coverage of the French case last year. But Siemionow and other physicians engaged in research on facial transplantation emphasize that, in reality, the procedure is far more complicated — surgically, immunologically, and psychologically — and the results more uncertain than its fictional portrayals suggest.

"Technically, it is very difficult, much more difficult than the hand," said Jean-Michel Dubernard, the French surgeon who pioneered both transplantation procedures. In addition, because nerves grow and heal slowly, sensation and mobility of the transplant, and thus the operation's technical success, cannot be fully assessed until nine months or longer after the procedure. Immunologically, transplanted skin triggers fiercer rejection than any other organ or tissue, so facial transplant recipients will have to

take immunosuppressants for life and undergo frequent medical monitoring. The consequences of not doing so were grimly brought home by a presentation that Guoxian Pei, a professor of orthopedics at Southern Medical University in Guangzhou, China, made at the Sixth International Symposium on Composite Tissue Allotransplantation, held in Tucson, Arizona, on January 17 and 18: of about a dozen hands that have been transplanted (some single and some bilateral) in China, Pei said, most have undergone chronic rejection with progressive loss of function because the recipients could not afford to continue to take immunosuppressants or did not receive regular medical follow-up. At least two patients had their transplanted hand amputated.

Psychologically, adjustment to a dramatically changed face will also be a gradual and potentially difficult process for recipients and their families. “We hope that, facing a mirror, the patient will be able to identify completely” with her new face, the French woman’s plastic surgeon, Bernard Devauchelle, told the audience of physicians at the Tucson symposium, seven weeks after the operation. “She now seems to be waiting, like the *Penseur* of Rodin, for the time when she will be able to smile.”

Siemionow, whose submission to the Cleveland Clinic IRB represented the culmination of 20 years of research, said that she is not intent on becoming the first physician to perform a full facial transplantation. “We are not rushing or jumping,” she said. “We want to be as thorough as possible, and really scientific.” She

is considering patients who have been severely disfigured by burns or trauma and who have some functional impairment, such as

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an inability to close their eyes or mouth. Such patients often have badly scarred faces that look like multicolored, immobile masks; features such as noses, eyelids, or lips may be missing or misshapen. Siemionow is also looking for people who have stable personalities and strong family support networks, yet are unhappy enough with their present faces to accept experimental surgery and a lifelong drug regimen that carries substantial risks of complications, such as cancer, infection, and diabetes. She estimates that there are thousands of severely disfigured people in the United States, many of them so socially isolated that they are invisible to the general public. Siemionow says she doesn’t want to perform the surgery on people who are able to live relatively comfortably with a traditionally reconstructed face. “Not every burn patient needs a face transplant. Our protocol is looking for the patients who have

already exhausted all reconstructive options. . . . They really don’t have faces.” The goal of surgery is to provide them with “a normal, human-looking skin and give them back their faces.”

There are additional requirements. Because Siemionow intends to transplant skin and subcutaneous tissue but not the underlying muscles, potential candidates will have to undergo electrophysiological testing of facial muscles to assess the degree of atrophy and evaluate how well their muscles may be able to “reanimate” the transplant. She explained that burn victims who are treated with partial-thickness skin grafts typically have progressive facial scarring that encases the underlying muscles, impairing their mobility, but that physical therapy can help to restore function. Potential candidates for a facial transplant must also have sufficient areas of intact skin elsewhere on their bodies to provide autologous grafts for a rescue operation, should the transplantation fail or the transplant be rejected. Siemionow estimates that the area needed to cover an entire face, scalp, front of the neck, and ears is about 1200 cm² of skin. Such a requirement eliminates many people with severe facial burns, who have often already undergone dozens of skin-graft operations, initially to replace the lost skin and later to deal with the scarring that inevitably occurs.

Moreover, any candidate who is chosen must be able to accept not only medical risks, uncertainty of success, and the likelihood of relentless media attention, but also the possibility that the operation may never take place at all: “They may understand that



Facial Flap Including Skin and Subcutaneous Tissue as It Might Look after Being Harvested from a Donor.

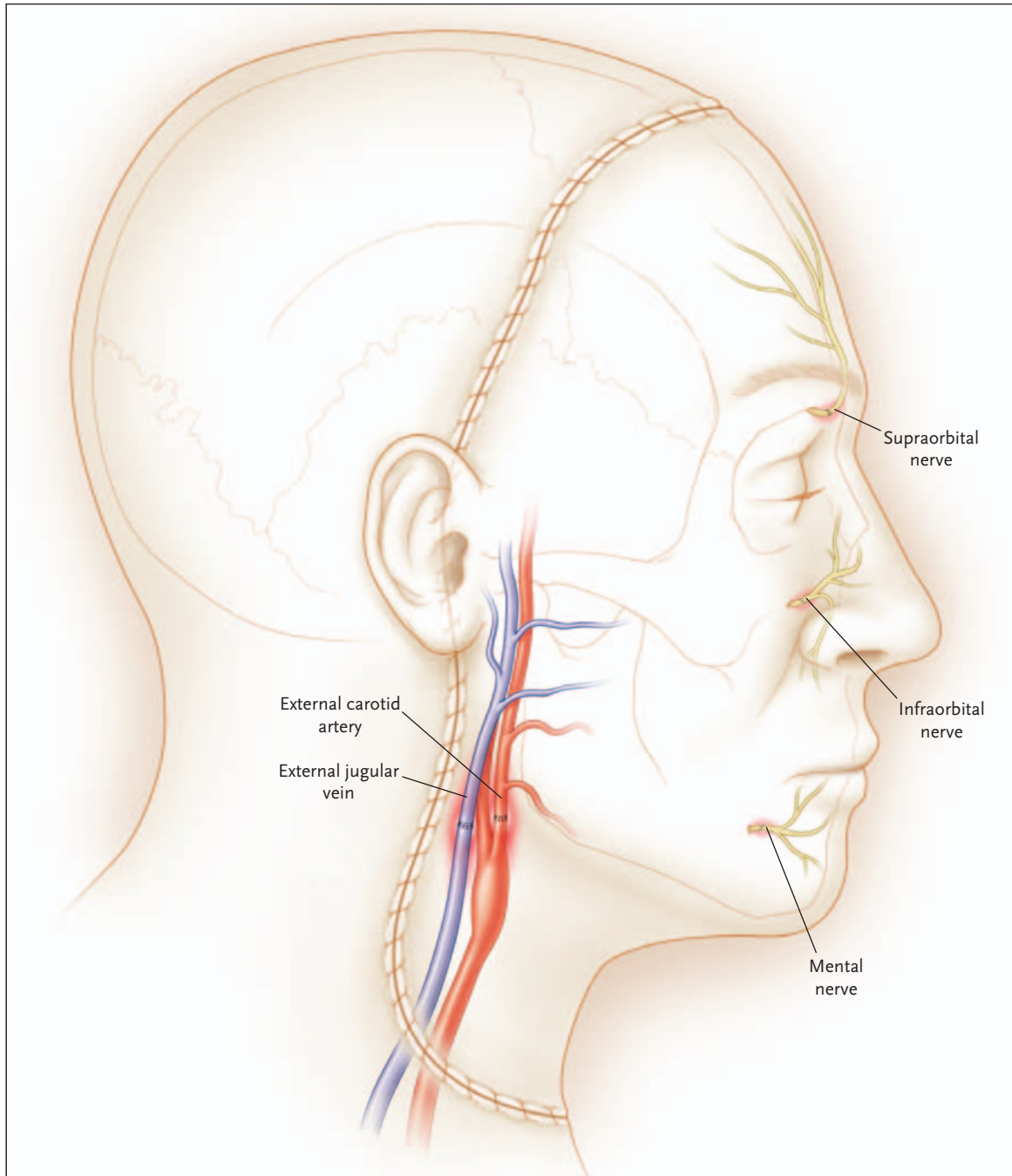
they have to wait a little bit, but they may not understand that it may be eternity — if there is no donor, for example,” Siemionow said. Potential candidates who are invited to the Cleveland Clinic will have psychiatric interviews and psychological testing, will meet with an ethicist, and will go through a detailed informed-consent process. Because adherence to the immunosuppressive regimen will be crucial to the survival of the transplanted tissue, the Royal Free Hospital’s Butler and psychologist Alex Clarke have used evidence from the transplantation literature to develop a compliance-screening tool that helps

them assess potential candidates’ personalities and predict their behavior as patients on the basis of their history and, in particular, how they adapted to their initial injury and its subsequent treatment. After the French transplantation, questions surfaced about the recipient’s mental health when her daughter told reporters that the dog bite had occurred after she had taken an overdose of sleeping pills in an apparent suicide attempt. “We would not probably have selected a patient with a previous suicide attempt unless it happened to be [during] a reactive depression, a self-terminating event,” Butler noted. Dubernard said in

January that his patient had resumed smoking while still hospitalized and recovering from her surgery, a habit that could compromise blood flow to the graft — and a behavior that Butler and Clarke’s compliance-screening tool might have predicted. On the other hand, Dubernard also reported that the patient had begun to go out in public and was gratified to find that her new face did not attract attention — suggesting that she was making progress incorporating her transformed countenance into her identity.

The surgical justification for trying a facial transplantation is that the texture and pliability of facial skin are unique. Grafts using skin from elsewhere on the body or prosthetic materials are an unsatisfactory substitute: although they cover the bones and muscle, they don’t look, feel, or move like a real face. In addition, efforts to reconstruct features such as lips or ears usually yield poor results. To be considered a success, transplantation would need to restore at least some facial mobility, imparting a degree of expression and function. A key question is whether the French partial transplantation or the full-face transplantations being planned by Siemionow and Butler will achieve that goal.

Siemionow’s approach is to harvest and transplant the entire facial flap and underlying subcutaneous tissue, along with its blood supply. She estimated that harvesting the flap from the donor will take 4 to 5 hours and that transplanting it will take 10 to 15 hours. Ten or more surgeons may participate in the dual operations. She plans to use major vessels in the neck — the external carotid



A Total Facial Transplant as It Might Look after Being Sutured into Place.

The approximate sites on each side of the neck are indicated, where the recipient's external carotid artery and external jugular vein would be anastomosed with the corresponding vessels in the graft. The supraorbital nerve, infraorbital nerve, and mental nerve on each side would be connected with the corresponding nerves in the transplanted tissue in order to provide sensation to the grafted skin.

arteries and external jugular veins — to connect the recipient's circulation to the graft. Once perfusion is established, she intends to connect several pairs of the recipient's sensory nerves to those in the transplanted tissue and to attach the transplanted skin flap to the underlying structures at the sites of various facial ligaments. She said that depending on the specific needs of the recipient, the graft may include lips, nose, or ears. However, both she and Butler said they hope to avoid transplanting facial muscles. Skin can survive ischemia for up to 13 hours, whereas muscle can survive for only about 6 hours. To include muscles would prolong the operation to harvest the tissue, potentially increasing the duration of ischemia, and would also complicate the transplantation surgery itself, since some of the recipient's own facial muscles would probably have to be removed. Removing them, in turn, would make a later rescue operation much more difficult in the event of rejection.

"The thing I'm worried about is, if it fails, what I'm going to be left with," Butler said. "My main concern is not to harm the patient." Moreover, transplanted muscles might not recover normal function: "Even if we take all the muscles, you never know how they will regenerate," noted Siemionow. "This is a little too risky to do all at once."

Chicago's Walton questions whether the proposed operation will work. He believes that it will be difficult to ensure an adequate blood supply to the graft without transplanting both the superficial and deep vessels that supply it. Such an approach would require

also harvesting the superficial myoaponeurotic system, a myofascial layer lying between the vessels that contains the muscles of facial animation. If a graft that includes this layer is laid over the recipient's own facial muscles, "how would the muscles in the patient's face be hooked up to the transplanted face?" he asked. "At best, you're going to have some-

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thing that looks a little bizarre. What you hope is you don't end up with a mask."

In the French operation, surgeons transplanted a triangle of tissue that included the lower part of the nose, the lips, and the chin, replacing tissue that had been destroyed as a result of the dog bite. The transplant contained skin, fat, and mucosa, as well as muscle groups that control the puckering and elevation of the lips. Surgeons attached the distal portions of some transplanted muscles to the proximal portions of the recipient's muscles. Although the woman's face looked impressively normal immediately after surgery, Walton noted that photographs taken in the weeks since have shown marked drooping of the lower lip. "Basically, her lips are paralyzed," he said. "Hopefully, with the residual muscle that's

hooked up to the transplant, she'll have some movement of the corners of her mouth."

The question of how the transplanted face will look is critical not only to the recipient, but also to the relatives of potential donors. "You would want to be sure that the family understands that the appearance of their loved one will not at all be replicated," said Eric D. Kodish, chairman of bioethics at the Cleveland Clinic Foundation and a member of the transplantation team. Butler has used a software program developed by forensic anthropologists to demonstrate to British transplantation coordinators that the new face will combine aspects of the donor and the recipient, with the underlying skeleton and muscles largely determining its shape and final appearance. "You don't get donor identity transplant, you don't get quite back to where you were. It's a hybrid," he said.

Finding donors may be the rate-limiting step in facial transplantation. In Cleveland, Siemionow plans to identify a candidate first, then work with the local organ-procurement agency to try to find a donor with a compatible blood group who matches the recipient's sex, race, and approximate age. Matching of HLA antigens will probably not be possible, although the French donor was a partial HLA match for the recipient. In France, unlike in the United States, the law presumes consent for organ donation, but Dubernard said that French surgeons nonetheless obtained the consent of the donor's family, and the donor's face was reconstructed afterward with the use of a silicone prosthesis.

In Louisville, Kentucky, where

the only two U.S. hand transplantations have been performed, difficulty in finding donors has been a principal reason why additional ones have not been done. Although two groups of surgeons in the city are eager to perform face transplantations, Paul O'Flynn, executive director of Kentucky Organ Donor Affiliates, said he anticipates that finding donors will be challenging. Of the 25,000 people who die in Kentucky hospitals each year, only about 200 are potential organ donors, because donors must be brain-dead and on a ventilator and must fulfill other criteria, such as not having cancer or various infections. Only about half of these potential donors' families consent to donation. The pool of potential tissue donors is smaller still, and obtaining consent for a facial transplantation is more problematic than for other tissues. "I have not laid the groundwork for approaching families about a face transplant," O'Flynn acknowledged in January.

For a transplant recipient, the primary long-term medical risks associated with the procedure are posed by the drugs needed to suppress the immune system and prevent rejection. Research in the field currently focuses on finding treatments that will induce specific tolerance to the transplanted tissue, with the goal of reducing or eliminating the need for such drugs. For example, Dubernard twice transfused his patient with hematopoietic stem cells from the facial-tissue donor 4 and 11 days after transplantation surgery, hoping to induce tolerance; still, she had a serious

episode of acute rejection about 3 weeks after the operation, which was treated with high doses of corticosteroids. As short-term induction therapy after transplantation, Siemionow plans to use antithymocyte globulin or specific antibodies against the T-cell-receptor complex — treatments that target T cells and help reduce the risk of acute rejection. The recipient will probably take tacrolimus, prednisone, and mycophenolate mofetil to maintain immunosuppression. Such a regimen costs between \$12,000 and \$24,000 per year and is associated with an increased incidence of infections, diabetes, cancer (especially squamous-cell carcinoma and lymphoma), renal and hepatic toxic effects, hypertension, disturbances in blood lipid levels, and other side effects.¹

A report published in 2004 by England's Royal College of Surgeons estimates that graft loss due to acute rejection might occur in approximately 10 percent of recipients within the first year and that substantial loss of graft function from chronic rejection might be expected in 30 to 50 percent of patients during the first two to five years.² The report concluded that current information on the risks of facial transplantation was inadequate with respect to informed consent and recommended that further research be done before full-face transplantation was attempted. The French National Ethics Committee and the American Society for Reconstructive Microsurgery (ASRM) have issued similar recommendations regarding full-face transplantation. However, in January, recog-

nizing that some U.S. groups are moving forward, the ASRM and the American Society of Plastic Surgeons jointly issued a set of guiding principles, urging that facial transplantation be attempted only by multidisciplinary teams under IRB-approved research protocols and only in patients who cannot be helped by traditional reconstructive surgery.³

Siemionow and her team at the Cleveland Clinic argue that those in the best position to accurately balance the risks and benefits of facial transplantation are the severely disfigured patients who are appropriate candidates — and that they deserve the opportunity to do so. "Only they are in a position to understand the benefit — and that doesn't disqualify them from assessing the risk," says the team's ethicist Kodish. "People with disfigurement this severe, you don't see them in the grocery store or the gas station. This is not a nose job . . . it's a medical procedure. I would really frame it the same way I would . . . the risks and benefits of a liver transplant or a heart transplant."

An interview with Dr. Siemionow can be heard at www.nejm.org.

Dr. Okie is a contributing editor of the *Journal*.

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